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F.D.A. tracked poison drugs, but trail went cold in China

By Walt Bogdanich
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After a drug ingredient from China killed dozens of Haitian children a decade ago, a senior American health official sent a cable to her investigators: find out who made the poisonous ingredient and why a state-owned company in China exported it as safe, pharmaceutical-grade glycerin.

The Chinese were of little help. Requests to find the manufacturer were ignored. Business records were withheld or destroyed.

The Americans had reason for alarm. "The U.S. imports a lot of Chinese glycerin and it is used in ingested products such as toothpaste," Mary Pendergast, then deputy commissioner for the Food and Drug Administration, wrote on Oct. 27, 1997. Learning how diethylene glycol, a syrupy poison used in some antifreeze, ended up in Haitian fever medicine might "prevent this tragedy from happening again," she wrote.

The FDA's mission ultimately failed. By the time an FDA agent visited the suspected manufacturer, the plant was shut down and Chinese companies said they bore no responsibility for the mass poisoning.

Ten years later it happened again, this time in Panama. Chinese-made diethylene glycol, masquerading as its more expensive chemical cousin glycerin, was mixed into medicine, killing at least 100 people there last year. And recently, Chinese toothpaste containing diethylene glycol was found in the United States and seven other countries, prompting tens of thousands of tubes to be recalled.

The FDA's efforts to investigate the Haiti poisonings, documented in internal FDA memorandums obtained by The New York Times, demonstrate not only the intransigence of Chinese officials, but also the same regulatory failings that allowed a virtually identical poisoning to occur 10 years later. The cases further illustrate what happens when nations fail to police the global pipeline of pharmaceutical ingredients.

In Haiti and Panama, the poison was traced to Chinese chemical companies not certified to make pharmaceutical ingredients. State-owned exporters then shipped the toxic syrup to European traders, who resold it without identifying the previous owner — an attempt to keep buyers from bypassing them on future orders.

As a result, most of the buyers did not know that the ingredient came from China, known for producing counterfeit products, nor did they show much interest in finding out.

China itself was a victim of diethylene glycol poisoning last year when at least 18 people died after ingesting poisonous medicine made there. In the wake of the deaths, and reports of pet food and other products contaminated with dangerous ingredients from China, officials there announced that they would overhaul the regulation of food, drugs and chemicals.

Beyond the three incidents linked to Chinese diethylene glycol, there have been at least five other mass poisonings involving the mislabeled chemical in the past two decades — in Bangladesh, Nigeria, Argentina and twice in India.

"This problem keeps coming back," said Dr. Joshua Schier, a toxicologist with the Centers for Disease Control and Prevention. And no wonder: the counterfeiters are rarely identified, much less prosecuted.

Finding a way to keep diethylene glycol out of medicine, particularly in developing countries, has confounded health officials for decades. "It is preventable and we have to figure out some way of stopping this from happening again," said Carol Rubin, a senior CDC official.

In a global economy, ingredients for drugs are often bought and sold many times in different countries, sometimes without proper paperwork, all of which increases the risk of fraud, the authorities say.

The Panama poison passed through five hands, the Haitian poison six. In both cases, the factory's original certificate of analysis, attesting to the contents of the shipment and its provenance, did not accompany the product as it moved around the world.

"Where there is a loophole in the system, a frailty in the system, it's the ability of an unscrupulous distributor to take industrial or technical material and pass it off as pharmaceutical grade," said Kevin McGlue, a board member of the International Pharmaceutical Excipients Council.

Uncovering that deception can be difficult. "It's impossible to get anyone to do the trace-backs," said Dr. Michael Bennish, co-author of a 1995 medical journal article on a poisoning epidemic in Bangladesh.

One reason, Bennish said, is the clout of local manufacturers. "We tried to follow up as amateur Sherlocks, investigators, but you don't go down to the wholesale market and ask questions," he said. "You are going to get your fingers burnt."

A Crisis in Haiti

By the end of June 1996, the FDA knew it might have an international crisis on its hands. A poison had found its way into fever syrup in Haiti, and the FDA wanted to know if more of the same might be heading to the United States or, for that matter, to any other country. But to learn that, the agency needed to find the manufacturer.

This was not just any poison. Virtually every young poisoning victim who showed up at the main hospital in Port-au-Prince, Haiti's capital, died.

Labeled pharmaceutical-grade glycerin, the toxic syrup was mixed into thousands of bottles of fever medicine. For months, parents gave it to their children, then watched them die, in agony, from kidney failure. No one suspected the medicine until much later.

Officially, at least 88 children died, nearly half under the age of 2. But those 88 were only the ones doctors remembered or for whom hospital records could be found.

The FDA traced the poison to a German broker, Chemical Trading and Consulting, but the company's records were not much help. "They cannot trace glycerine lots to their manufacturer," David Pulham, an FDA investigator, wrote on June 30, 1996.

Chemical Trading had arranged for a Dutch company, Vos BV, to sell 72 barrels of the suspect syrup to Haiti, records show. The agency dispatched an investigator, Ann deMarco, who made an unsettling discovery — sitting in Vos's warehouse near Rotterdam, were 66 more barrels labeled glycerin, all containing lethal concentrations of diethylene glycol.

"Some of this second shipment has been sold," deMarco wrote in a memorandum on July 4, 1996. Although the missing barrels had gone to an industrial user, not a drug maker, the FDA's worries grew.

deMarco learned that another broker, Metall-Chemie, a German trader, had arranged for Vos to buy the barrels from Sinochem International Chemicals Company, a giant exporter in Beijing owned by the Chinese government.

But Metall-Chemie also did not know the manufacturer, and one of its officials predicted that the FDA

would have trouble finding that out. "It is difficult to get any information from Chinese traders," deMarco wrote.

More complete shipping records would have identified who made the poison. But in this case, records provided few clues.

"The original source of the material had been obliterated on documents and product containers," deMarco wrote to senior FDA officials. "One trader referred to this practice as 'neutralization.' I was advised that neutralization is a common practice among traders in order to protect their business interests."

With no paper trail, American officials turned to Sinochem for help.

Initially, they took an indirect approach. In July 1996, the American Embassy in China contacted the company and asked for a list of Chinese glycerin makers, without saying that it was investigating the Haiti poisonings. Sinochem, however, "would not reveal the names of actual manufacturers in order to prevent the prospective foreign customer from bypassing Sinochem," an embassy official reported to Washington.

In early August, American officials asked Sinochem representatives specifically about the origin of the Haiti poison. "They want to investigate further and were unable (or unwilling) to give the name of the manufacturer at this time," the officials reported.

U.S. investigators sought help from senior Chinese drug regulators, who promised to help find the manufacturer, but said it "will take time," records show.

When another month passed without any word from either regulators or Sinochem, the embassy tried again. Chinese regulators said they had done nothing to find the factory, according to a confidential State Department telegram from September 1996.

Sinochem did finally offer the manufacturer's name: the Tianhong Fine Chemicals Factory in the city of Dalian in northeastern China. But Sinochem "refused" to provide an address, saying it was illegible. A telephone number would have to suffice, it said.

That, too, was unproductive. When American investigators called the plant manager, Zhang Gang, they were told he was not available. Send a fax, they were told. That did not work either. "The phone was always busy," investigators reported.

Finally, they got Zhang on the phone, but he, too, refused to give out his factory's address. He said tests had found no signs of diethylene glycol, adding that "there had been no cases in China of poisoning resulting from the ingestion" of glycerin contaminated by diethylene glycol, investigators wrote.

After months of trying to trace the poison to its source, United States investigators were at a dead end.

"The Chinese officials we contacted on this matter were all reluctant to become involved," a State Department official wrote in late September 1996, saying that drug regulators and the plant manager had insisted on communicating only on the telephone "to avoid leaving a paper trail."

He added, "We cannot be optimistic about our chances for success in tracking down the other possible glycerine shipments."

The following May, Pulham, who was part of the original FDA investigative team in Haiti, tried to revive the investigation. "Is it possible to block-list all Chinese pharmaceutical products until we gain cooperation?" he asked.

The suggestion went nowhere. Five months later, Pendergast of the FDA wrote her memorandum, imploring investigators to keep digging.

"China is turning into one of the major bulk pharmaceutical producers in the world," she wrote. "Unless they have an open, transparent and predictable system for dealing with problems and other countries, it is going to be rough sledding in the years ahead."

On Nov. 17, 1997, U.S. investigators once again questioned Sinochem officials. They denied any wrongdoing, saying that two certificates of analysis showed that the suspect shipment was safe, pharmaceutical-grade syrup. But when the FDA asked to see them, Sinochem refused.

"The officials were not willing to explain why they could not provide the copies," an American official reported at the time.

Chen Liusuo, who handled the glycerin sales, strongly disputed the FDA's account. In an interview with The Times, Chen said Sinochem cooperated. "We gave them everything they wanted," Chen said, adding that the agency was satisfied.

"The product we sold was glycerin," he said. "It passed through three or four companies after us. To find the problem you need to look at every link in the supply chain."

A Chinese government official familiar with the FDA's inquiries said the Americans' frustration might have stemmed from their misunderstanding about who regulated chemical companies, which led them to seek help from the wrong officials. "This was a truly tragic event, and we expressed our sadness and sympathy," said the official, who asked not to be identified.

At the end of 1997, a year and a half after the FDA began tracing the poisonous shipments, one of its investigators, Ted Sze, finally got inside the Tianhong chemical plant in Dalian. But glycerin was no longer made there, and Sze had no records to inspect. The plant manager, Zhang, told investigators that he had received no complaints about his products and that his company had not produced the poison.

Sze, now retired from the FDA, said in an interview that he had no choice but to accept the manager's word and clear the company of wrongdoing. "By the time I went there, the plant was already shut down," he said. "The agency can only do so much."

The Experts' Recommendations

The United States may not have gotten what it wanted from China, but the Haiti crisis did bring together health groups to search for ways to stop diethylene glycol poisonings. At a workshop in Washington in February 1997, health experts recommended that certificates of analysis be improved to allow users to "trace the product back through every intermediary, broker and repackager to the original manufacturer."

The workshop participants also called for better testing of drug ingredients and asked governments to tighten oversight of drug manufacturing.

The next year, the World Health Organization offered many of the same recommendations. And a 1998 article in JAMA, the Journal of the American Medical Association, warned that failure to strictly follow the guidelines could cause poisonings "even in countries where quality control procedures are usually strictly applied."

Much of this had been said before, yet the poisonings have continued.

Just as the JAMA article was being published, three dozen children began dying of acute renal failure at two hospitals in Delhi, India. A local drug maker had unwittingly mixed diethylene glycol into acetaminophen syrup, much as the Haitian pharmacist had.

The drug maker was prosecuted, but according to interviews and government records no progress had been made in identifying the supplier of the poison.

"My experience as an investigator tells me that many of these things will not be proven," said Dr. M. Venkateswarlu, the drug controller general of India.

Finding counterfeiters often means pursuing leads across foreign borders, and no international authority has the power to do that. Dr. Howard Zucker, who helps to oversee drug issues for the WHO, said individual countries must conduct their own trace-back investigations.

But if the United States could not do that on behalf of Haiti, poorer, less influential nations would have little chance of tracking down counterfeiters.

After the Haiti poisoning, a more accurate, less expensive test for diethylene glycol was developed, but last year's case in Panama shows that suppliers and governments do not always use it.

And as long as counterfeiters do not fear prosecution, the poisonings are likely to continue, experts say.

Dr. Mohammed Hanif, a prominent physician in Dhaka, Bangladesh, said the foreign suppliers of diethylene glycol were never prosecuted for the deaths of thousands of children from 1982 to 1992. "The traumatizing memories of those days still torment me," said Hanif, who wrote a paper about the deaths from toxic medicine.

In Argentina, a court official said no one had been prosecuted for supplying the diethylene glycol that ended up in a health supplement, killing 29 people in 1992.

David Mishael, a Miami lawyer, knows the difficulty of assigning blame in these deaths. For 10 years, Mishael has unsuccessfully pursued legal claims in the United States and Europe against European traders that helped to arrange the shipment of toxic syrup to Haiti. "You can imagine the cost," said Mishael, who is representing Haitian parents whose children died from the fever medicine.

He said Dutch authorities assessed a $250,000 fine against Vos, which tested the counterfeit syrup, found it impure and did not alert anyone in Haiti. But given how many died, he called the size of the fine "a joke." A lawyer who represents Vos, Jeffrey Shapiro, declined to comment.

A few children survived after being flown to the United States by humanitarian groups. One of them, Faika Jean, was 2 months old at the time and nearly died en route. Now 11, she has learning disabilities as a result of the poisoning, said her father, Wislin Jean.

Pendergast, now a private lawyer and consultant, said China had the most to answer for. "Everybody else is just reacting to initial failures," she said. "It needs to take steps to protect not just its own consumers but also consumers all around the world."

After The Times reported in May that the Panama poison had been made and exported by Chinese companies as 99.5 percent pure glycerin, Chinese regulators said they would reopen their investigation of the incident. Three weeks later, the officials acknowledged some "misconduct" in how Chinese companies labeled the toxic syrup.

But most of the blame, they said, rested with a Panamanian importer who changed the paperwork to make the syrup look safer than it actually was.

The FDA disagrees, saying the deception began with Chinese companies falsely labeling a poisonous product glycerin. "If the drums had been 99.5 percent glycerin, the deaths in Panama would never have occurred," the FDA said in a statement.

A Dissatisfied Customer

The FDA's Haiti investigation never did find more counterfeit glycerin from China, despite a global hunt. But its concerns, it turns out, were not unfounded.

In 1995, the same year babies began to die in Haiti, 284 barrels of a chemical labeled glycerin arrived in New York on container ships. Although the chemical was not intended for use in drugs, it was labeled 98 percent pure. An official with the company that bought the barrels, Dastech International, of Great Neck, New York, would later say, "It smelled like glycerin, it looked like glycerin." But after one of its customers complained, Dastech took a closer look.

Although the chemical was labeled 98 percent pure glycerin, Dastech said in court records that the syrup actually contained sugar compounds — as well as diethylene glycol.

The exporter was Sinochem. Claiming that it was fleeced, Dastech tried to get its money back from the broker who arranged the sale, court records show.

It never did.

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